09767460 ,070301

Howrey Docket No.: 01561-0002-CPUS01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE THE APPLICATION OF: **Mandell et al.**

SERIAL NO.: **09/767,460**

FILED: **JANUARY 23, 2001**

FOR: **ALGORITHMIC DESIGN OF PEPTIDES FOR BINDING AND/OR MODULATION OF THE FUNCTIONS OF RECEPTORS AND/OR OTHER PROTEINS**

ART UNIT: **1646**

EXAMINER: NOT YET ASSIGNED

Response to Notice to Comply with Requirements for Patent Applications Containing Nucleotide and/or Amino Acid Sequence Disclosures

Commissioner for Patents
Washington, D.C. 20231

Sir:

This is in response to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures, dated May 3, 2001. Please amend the specification and claims of the above-identified application, as indicated below.

CERTIFICATE OF MAILING
(37 C.F.R. §1.8a)

I hereby certify that this paper (along with any referred to as being attached hereto) is being deposited with the United States Postal Service on the date shown below with sufficient postage as First Class Mail in an envelope addressed to the Commissioner for Patents, Washington, D.C. 20231

June 29, 2001
Date of Deposit

Nora Durant
Name of Person Mailing Paper

Nora Durant
Signature of Person Mailing Paper

In the Specification

Please delete the first complete paragraph, page 71, lines 11-14, and replace with:

"As an example of redundant substring template generation, consider the following short amino acid sequence retained as a string vector of amino acid one letter representations:

AIRCKSMLRYGHAMQLREWVCCMHAMQVYRLM (SEQ ID NO:94)"

Please delete the second complete paragraph, page 71, line 15 to page 72, line 3, and replace with:

"If we chose to apply the template-generating algorithm directly to this series, the search algorithm would begin by looking for two copies of the first half of the series, AIRCKSMLRYGHAMQL (SEQ ID NO:95). Next it would assess the starting positions and frequency of occurrence of the substring from which the last amino acid, L has been dropped, i.e., AIRCKSMLRYGHAMQ (SEQ ID NO: 96), and so on, looking at each possible substring in the first half of the sequence. The algorithm finds one redundant substring, HAMQ, occurring twice starting at positions 12 and 24. A generalization of this method also allows for the search of substrings that are both "backward" and "forward" in orientation in the original sequence. Such a search of our example string also turns up the twice repeated substring MLRY, appearing at starting position 7 in a "forward" orientation and at starting position 29 in a "backward" orientation. Our R_{temp} might then equal one or both of these specific amino acid substrings in some order and orientation."

Please delete the second complete paragraph, page 80, line 18 to page 81, line 17, and replace with:

"Figures 4A-4D summarize the EAR responses to dopamine infusion with respect to the influence of SHQR (SEQ ID NO:1) and THQA (SEQ ID NO:2) in the two D_2DA receptor-transfected cell systems, in which the former significantly potentiated the dopamine-induced increment in total milli-pH units in both cell systems. We report the results of one-tailed t-tests with pairing within chamber as $t_{(\#)}$, where # represents the degrees of freedom of the paired comparison and ρ denotes the probability of such results occurring by chance. For the SHQR peptide (SEQ ID NO:1) in the LtK system, $t_{(3)} = 13.28$, $\rho = 0.0009$, and for the SHQR peptide (SEQ ID NO:1) in the CHO cell system, $t_{(3)} = 28.06$, $\rho < 0.0001$. THQA (SEQ ID NO:2) did not significantly potentiate the dopamine response in either system, $t_{(3)} = 0.620$ and $t_{(3)} = 1.309$, $\rho > 0.05$, respectively. Figures 5A-5D contain graphs of the influence of the peptides E...PL (SEQ ID NO:3) and E...PY (SEQ ID NO:4) on the EAR response to dopamine in the two D_2DA receptor-transfected cell systems. Both peptides demonstrated statistically significant activation, $t_{(7)} = 25.47$, $\rho < 0.0001$ and $t_{(3)} = 69.830$, $\rho < 0.0001$, respectively, in the LtK system. However, neither of the E...PL (SEQ ID NO:3) and E...PY (SEQ ID NO:4) peptides influenced the dopamine-induced EAR of the CHO cells significantly, with $t_{(3)} == 1.542$, $\rho > 0.05$ and $t_{(7)} = 1.283$, $\rho > 0.05$, respectively. Three of the remaining eight peptides exhibited statistically significant effects on at least one of the two receptor-transfected cell systems (Table 3). The overall "hit rate", as measured by modulation of the kinetics of the EAR of two transfected cell lines to dopamine, for these peptides was thus 50% (i.e., six of twelve peptide candidates that were synthesized and tested statistically significantly altered EAR in one or both of the D_2DA receptor-transfected cell

systems used). All D_2DA targeted peptides whose effects reached significance increased EAR."

Please delete the first complete paragraph, page 81, lines 18-22, and replace with:

"A set of EAR dose response curves were computed for the SHQR peptide (SEQ ID NO:1) across concentrations of dopamine ($10^{-8\,5}$ M to $10^{-5.5}$ M) and the SQHR peptide (SEQ ID NO:1; 10 nM to 3 μM) (not shown). LtK cells were used for these experiments. The resulting dose response curves manifested asymptotic sigmoidal kinetics, suggestive of positive cooperativity.

Please delete Table 7, page 88, and replace with:

Examples of Human Calcitonin-Targeted Peptides from Non-Overlapping Redundant Substring Template of Human Calcitonin					
SEQ ID	**Sequence**	**SEQ ID**	**Sequence**	**SEQ ID**	**Sequence**
34	KPNLPNELNK	54	VGTLNPAFSV	74	MNSIQTDFTM
35	VTNLGNHIGV	55	CGNYGTRFSK	75	VQSLTNDISK
36	CNNFSPDITV	56	CSSLQQALTV	76	KGNINPAYNV
37	MQQITTHFQC	57	MPSIPTHLNK	77	KTGLNNEINV
38	VNTFGTELSC	58	KNNYGQAFTV	78	VQSFTNEIQC
39	CNNIGNRLSC	59	KNQLNTEINC	79	KTTINGHISK
40	KGNFTPEWPC	60	KNPLNNHLNM	80	VGGYGTDYNM
41	MGPLPQAFQC	61	VNGIGQAINV	81	MQGYTNDIPV
42	KSNIGPALTM	62	CPGITGDFQK	82	VNQWQNHYTM
43	VSQYGQELQV	63	MTQFQSHITV	83	KPTFSNAYNV
44	VSPYQSHFNV	64	VQTYPPHFPV	84	VTNFSNALSM
45	MGGWGPALNC	65	KGNLNTDLNM	85	VTPINSEFPC
46	CTGYTNAIQM	66	VTPLSSAINK	86	KNQLNTHIGK
47	MNTLQQAYPK	67	VNNLSSEYNV	87	VQSINNAIGK
48	VQPYNGELNM	68	MPPWPSDYPC	88	MGTFQPDWQV
49	VTNWNGRINK	69	KQSFQSELNK	89	VQTISSRWGK
50	MQNFPTAINV	70	VPSLTTRLQV	90	MGNITQDLQC
51	VPSIQGHYGM	71	VQPLQGHLPV	91	KGSYTTELGV
52	VGNLTQHYTK	72	VSQFNQAWGV	92	KNSYSPELTV
53	VPPFTNHWQK	73	VPSLNSALGV	93	CNSYTPEFPC

Version with Markings to Show Changes Made

1st complete paragraph, page 71, lines 11-14:

"As an example of redundant substring template generation, consider the following short amino acid sequence retained as a string vector of amino acid one letter representations:

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38	VNTFGTELSC	58	KNNYGQAFTV	78	VQSFTNEIQC
39	CNNIGNRLSC	59	KNQLNTEINC	79	KTTINGHISK
40	KGNFTPEWPC	60	KNPLNNHLNM	80	VGGYGTDYNM
41	MGPLPQAFQC	61	VNGIGQAINV	81	MQGYTNDIPV
42	KSNIGPALTM	62	CPGITGDFQK	82	VNQWQNHYTM
43	VSQYGQELQV	63	MTQFQSHITV	83	KPTFSNAYNV
44	VSPYQSHFNV	64	VQTYPPHFPV	84	VTNFSNALSM
45	MGGWGPALNC	65	KGNLNTDLNM	85	VTPINSEFPC
46	CTGYTNAIQM	66	VTPLSSAINK	86	KNQLNTHIGK
47	MNTLQQAYPK	67	VNNLSSEYNV	87	VQSINNAIGK
48	VQPYNGELNM	68	MPPWPSDYPC	88	MGTFQPDWQV
49	VTNWNGRINK	69	KQSFQSELNK	89	VQTISSRWGK
50	MQNFPTAINV	70	VPSLTTRLQV	90	MGNITQDLQC
51	VPSIQGHYGM	71	VQPLQGHLPV	91	KGSYTTELGV
52	VGNLTQHYTK	72	VSQFNQAWGV	92	KNSYSPELTV
53	VPPFTNHWQK	73	VPSLNSALGV	93	CNSYTPEFPC

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Remarks

No new matter is being added by these amendments. Corrections in the specification add SEQ ID NO's where appropriate. In addition, a sequence listing is being submitted to reflect the omission of the sequence listing in the original filing. The Applicants respectfully request that the above amendments be entered into the application.

Respectfully submitted,

Date: June 29 2001

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